Rare disease

Pemphigoid gestationis

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Correspondence to Céline M J G Lardenoije, c.lardenoije@orbisconcern.nl**Summary**

A 39-year-old woman in the 39th week of her fifth pregnancy presented with severe itching. In recent weeks she had developed an increasingly itchy rash on her trunk and arms. Upon examination we observed multiple erythematous plaques and vesicles. Histological examinations of two skin biopsies confirmed the diagnosis of pemphigoid gestationis. Because the patient's complaints worsened we decided to deliver the baby, and as it was in transverse lie this was by caesarean section. A healthy son without rash was born. Although pemphigoid gestationis occurs in only 1 in 50 000 pregnancies, it is very important to be aware of this condition when a pregnant woman has itching. Not recognising pemphigoid gestationis may lead to inadequate maternal treatment and possible preterm birth and neonatal pemphigoid gestationis.

BACKGROUND

Pemphigoid gestationis is a rare but important cause of itching in pregnant women. Given that itching is a common and often harmless complaint in pregnancy, it is often ignored (obstetric cholestasis, which causes itching without rash, may similarly be missed). If general practitioners and other specialists are not aware of this condition, the pregnant woman will not receive adequate treatment, possibly leading to preterm birth and neonatal pemphigoid gestationis. The aim of this communication is to increase awareness among clinicians of the diagnosis of pemphigoid gestationis in a pregnant woman with itching.

CASE PRESENTATION

A 39-year-old woman in her fifth pregnancy presented to the obstetrics department with severe itching.

The obstetric history showed four uneventful pregnancies and deliveries. At 39 weeks' gestation, the patient suddenly developed an increasingly itchy rash over her whole trunk which spread to the arms (figure 1). She did not have fever or feel ill. There was no history of allergic reactions. Triamcinolone, lidocaine and menthol cream had been given to the patient by her general practitioner, but all were ineffective.

INVESTIGATIONS

On physical examination we observed a pregnant woman with a fundal height according to a gestational age of 39 weeks. The fetus was in good condition. We observed multiple erythematous plaques and vesicles over the entire trunk and arms (figure 2). There were no blisters or pustules. Laboratory examination did not show any abnormalities (no eosinophilia, and normal infectious parameters, liver function and bilirubin).

Abdominal ultrasound showed a normal fetus lying in a transverse position. Two skin biopsies, one of the arm and one of the trunk, were performed by a dermatologist.

Histological examination confirmed the diagnosis of pemphigoid gestationis.

DIFFERENTIAL DIAGNOSIS

- pemphigoid gestationis
- erythema exsudativum multiforme.

TREATMENT

Because the patient's complaints worsened we decided to deliver the baby, by caesarean section as it was in transverse lie. A healthy son of 3380 g without rash was born.

OUTCOME AND FOLLOW-UP

After the baby was born, all skin lesions disappeared in a couple of days. Afterwards the patient had no further complaints.

DISCUSSION

Pemphigoid gestationis, previously referred to as herpes gestationis, is a rare autoimmune disease of pregnancy and the postpartum period. Despite its name, herpes gestationis is not related to herpes virus infections (the old term reflects the occurrence of herpetiform lesions). Pemphigoid gestationis occurs in approximately 1 in 50 000 pregnancies,¹ and characteristically appears during the second or third trimester. In rare cases, it starts in the first trimester or in the postpartum period.

Pemphigoid gestationis may occur in association with other autoimmune diseases, trophoblastic tumours, hydatiform mole and choriocarcinoma.^{2–5} Women with a history of pemphigoid gestationis are at higher risk of developing Graves' disease.^{2,6}

The aetiology of pemphigoid gestationis is not completely understood. It is presumed that auto-antibodies are formed against the placenta. These auto-antibodies then cross-react with an antigen on the basement membrane of the skin. This immune response is mainly directed towards the bullous pemphigoid antigen with a molecular weight of 180 kDa, bp 180.^{7,8} A lesser immune response is also directed against bp 280.⁹ Blistering of the skin occurs as a consequence of this autoimmune reaction.

The reaction of antibodies on the skin is identical to the reaction seen in parapemphigus.

Figure 1 Pemphigoid gestationis on the abdomen.

Figure 2 Pemphigoid gestationis on the arms.

Pemphigoid gestationis usually starts with intense itchy erythematous papules and plaques around the umbilicus which quickly spread to the abdomen, back, chest and extremities, sparing the face, mucosal surfaces, palms and soles.^{6 10 11} Later, blisters filled with clear liquid are formed, although in some cases blisters may be absent.¹²

Classic histopathological findings in pemphigoid gestationis are subepidermal vesicles, with lymphocytes and eosinophils in a perivascular distribution within the dermis. The presence of eosinophils is the most constant feature of the histopathological appearance of pemphigoid gestationis.^{13 14}

Symptoms in the early stage of the condition can be similar to those of pruritic urticarial papules and plaques of pregnancy (PUPP), which is a more common cause of itching during pregnancy.¹⁵ PUPP differs from pemphigoid gestationis in that it lacks both blisters and an autoimmune response.

The diagnosis of pemphigoid gestationis can be made from the general clinical image and can be confirmed by immunoblotting or ELISA, both of which are sensitive methods to prove auto-antibodies against bp 180. Investigations showed that in patients with pemphigoid gestationis auto-antibodies against bp 180 were detected

in 93% of cases by immunoblotting and in 86.3% by ELISA.¹⁶ The severity of the disease may be correlated with the auto-antibodies detected by ELISA and/or eosinophilic leukocytosis.^{16 17}

The typical finding at immunofluorescence is the C3 complement component, and in 25% immunoglobulin G (IgG) in a linear band along the basement membrane.^{13 18–21}

Pathophysiologically, the antibodies bind to the basement membrane which causes a complement activation through the classical complement pathway. Chemoattraction of eosinophils and their subsequent degranulation then take place.^{13 22} This presumably happens due to the release of proteolytic enzymes from eosinophilic granules that dissolves the bond between the dermis and epidermis.¹³

An IgG serum antibody is almost always found by indirect immunofluorescence, even when IgG is not seen by direct immunofluorescence. The circulating IgG antibody which fixes complement at the basement membrane is designated the herpes gestationis factor.^{13 18–20 23}

Immunogenetic examination has shown an increase in the HLA antigens DR3 and DR4 in patients with pemphigoid gestationis: 61–80% have DR3, 52–53% have DR4 and 43–50% have both.^{6 24}

Treatment of pemphigoid gestationis starts with application of topical corticosteroids and/or lotions to decrease itch. Antihistamines can also help to control itching. In patients with severe symptoms, systemic steroid therapy is needed.²⁵ If these treatments are ineffective, plasmapheresis, cyclophosphamide, ciclosporin and dapsone are reported to be useful.^{26 27} However, their side-effects harm the mother and child.^{28 29}

Generally, pemphigoid gestationis tends to exacerbate after birth (75% of patients flare post partum).¹³ The duration of active disease ranges from 2 weeks post partum to 12 years post partum.¹⁰ In addition, some women experience recurrence of disease when taking oral contraceptives or during menses.^{17 23 30 31} In one study recurrence of pemphigoid gestationis was found in 12% of women during menstruation.¹⁷

The possibility that pemphigoid gestationis will recur again in a subsequent pregnancy is high at almost 90%, and usually occurs earlier in pregnancy and is more severe.¹³ Sometimes it may skip pregnancies.¹⁰

There is no consensus about the influence of a new partner on the risk of pemphigoid gestationis in following pregnancies. Some reports describe reducing prevalence with a new partner, while others find no differences.^{1 10}

Pemphigoid gestationis should be considered as an indication for a clinical delivery.

Approximately 10% of all neonates of mothers with pemphigoid gestationis have cutaneous lesions similar to pemphigoid gestationis.¹³ The disease in children seems to originate from passive transfer of the pemphigoid antibodies, but could also be caused by resting maternal hormones.¹ The skin lesions resolve spontaneously in the first months.³² Immunofluorescence of the newborn skin may be positive, even when there are no clinical symptoms of the disease.^{18 33 34} When high doses of corticosteroids are given during pregnancy, the newborn baby must be examined immediately after delivery. Adrenal insufficiency has to be excluded, especially if the mother has used corticosteroids for a long period.³⁵ Besides, dapsone may cause

haemolytic disease in the child.³⁶ Whether pemphigoid gestationis itself leads to complications in the child is still unclear.

Study of neonatal complications showed that there was morbidity or mortality in 38% of cases of pemphigoid gestationis: premature partus in 23%, neonatal herpes gestationis in 9% and intrauterine death in 7.7%.¹⁷ A relationship between pemphigoid gestationis and prematurity was also found in other studies.^{2 37} Shornick and Black showed that 16% of pregnancies associated with pemphigoid gestationis ended before 36 weeks and 32% before 38 weeks, compared to 2% and 11% in uncomplicated pregnancies.² Further, a link was shown between pemphigoid gestationis and lower birth weight. This could be a consequence of mild placental insufficiency through an immune response between placental antigens and antibodies against the skin.³⁸ Shornick and Black did not find an increase in spontaneous abortions or stillbirths in patients with pemphigoid gestationis, nor did the use of systemic steroids appear to influence the risk of preterm birth or lower birth weight.³⁹

There is no evidence in the literature that pregnancy should be ended because of neonatal risks, likely due to the fact that most studies do not find an elevated risk of stillbirth. We do not think it necessary to induce labour, but advise close monitoring by regular ultrasound in case of low birth weight. Furthermore, it is important to be aware of the risk of preterm birth.

Learning points

- Be aware of the possibility of pemphigoid gestationis in a pregnant woman with itching.
- A pregnant woman with pemphigoid gestationis should be treated in hospital, and closely monitored because of the elevated risk of preterm birth and low birth weight.

Competing interests None.

Patient consent Obtained.

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